Editorial

Thrombi and Neutrophils

Jean-Baptiste Michel, Benoît Ho-Tin-Noé

More than a century ago, in 1881, Bizzozero1 discovered platelets and their role in primary hemostasis. Since this founding study, it has been shown that, in addition to the scaffold of platelets and fibrin, other proteins and cells play an important role in thrombus formation and stabilization. One can already observe in the previous drawings of Bizzozero1 that leukocytes and red blood cells are trapped within the thrombus. We know now that thrombi are actually heterogeneous and can take on multiple forms both in the arterial and venous systems. As a consequence of this diversity, thrombi can have a variable effect on the development and outcome of cardiovascular diseases. In fact, whereas occlusive thrombi can abruptly cause dramatic acute ischemic events, nonobstructive thrombi, like those found in abdominal aortic aneurysms, can slowly and progressively degrade the vessel wall via convection of blood-borne and leukocyte-derived proteases.2 Furthermore, thrombus heterogeneity bears important clinical implications because the efficacy of thrombolysis in the treatment of acute ischemic events is highly dependent on thrombus composition and structure. For example, both platelet-rich thrombi and aged thrombi are known to be more resistant to the gold-standard thrombolytic agent, recombinant tissue plasminogen activator (r-tPA).3 Because of these barriers to r-tPA–induced thrombolysis and given that r-tPA targets the fibrin scaffold, it has been proposed that targeting other thrombus components (eg, Von Willebrand factor)4 could help to improve the efficacy of thrombolysis.

Article, see p 1182

In recent years, neutrophil extracellular traps (NETs) have been identified as major triggers and structural factors of various forms of thrombosis, including infection-induced thrombosis,5 deep vein thrombosis,6 and cancer-associated thrombosis.7 NETs are extracellular webs primarily composed of DNA from neutrophils that ensnare pathogens but also cause platelet activation and aggregation.8,9 It should be noted that the discovery of NETs and of their role in thrombosis somewhat rehabilitates the theories of Schmidt10 and Mantegazza11, who both attributed triggering and structural factors to r-tPA–induced thrombolysis and given that r-tPA targets the fibrin scaffold, it has been proposed that targeting other thrombus components (eg, Von Willebrand factor)4 could help to improve the efficacy of thrombolysis.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the UMR 1148, Inserm-Laboratory for Vascular Translation Science, Denis Diderot Université, Paris, France.

Correspondence to Jean-Baptiste Michel, MD, PhD, UMR 1148, Inserm-Denis Diderot Université, CHU Xavier Bichat, 46 rue Henri Huchard, 75018 Paris. E-mail jean-baptiste.michel@inserm.fr (Circ Res. 2015;116:1107-1108. DOI: 10.1161/CIRCRESAHA.115.306050.) © 2015 American Heart Association, Inc. Circulation Research is available at http://circres.ahajournals.org DOI: 10.1161/CIRCRESAHA.115.306050

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the UMR 1148, Inserm-Laboratory for Vascular Translation Science, Denis Diderot Université, Paris, France.

Correspondence to Jean-Baptiste Michel, MD, PhD, UMR 1148, Inserm-Denis Diderot Université, CHU Xavier Bichat, 46 rue Henri Huchard, 75018 Paris. E-mail jean-baptiste.michel@inserm.fr (Circ Res. 2015;116:1107-1108. DOI: 10.1161/CIRCRESAHA.115.306050.) © 2015 American Heart Association, Inc. Circulation Research is available at http://circres.ahajournals.org DOI: 10.1161/CIRCRESAHA.115.306050

One of the strengths of the study by Mangold et al13 resides in the use of human biological material. When compared with mice, in which the blood count is low in granulocytes (<20%), polymorphonuclear neutrophils are the predominant type of circulating leukocytes (50%–70%) in humans and are therefore systematically present in human thrombi.16 Concordantly, important ancillary results of Mangold et al11 highlight the fact that neutrophils and NETs are significant components of human coronary thrombi that do not only represent new therapeutic targets for thrombolysis but also provide a source of new biomarkers to define the biological process of acute coronary syndrome. In fact, the authors show that measurement of free double-stranded DNA can be used as a plasma biomarker of coronary thrombus NET burden, in addition to the more classical markers of neutrophil activation (neutrophil elastase and myeloperoxidase).
Because pathogens are one of the strongest triggers of NET formation and to explain the observed activation of neutrophils at the culprit lesion site, the authors explored the thrombus content in bacterial species from the buccodental microbiome. Their results confirm the high frequency of contamination of coronary thrombi by weak buccodental pathogens, such as Streptococcus species. Oral bacteria have been detected in carotid endarterectomy samples and in thrombectomy samples. If one considers the effect that bacteria can have on the deleterious biological activities of thrombi, one can imagine that thrombus contamination also fosters thrombus- and neutrophil-dependent injury in ST-elevation acute coronary syndrome. Human abdominal aortic aneurysms, intracerebral aneurysms, and infective endocarditis nicely illustrate how interactions between bacteria and the thrombus can fuel thrombus-dependent injury, notably by promoting neutrophil recruitment and activation.

Conclusions and Perspectives

Intravascular thrombi, whatever their initial cause and localization, are highly pathogenic because they not only induce downstream tissue ischemia by occluding arteries but also participate in injury of the surrounding tissue by releasing proteolytic and oxidative enzymes. Because of the various mechanisms of resistance to thrombolysis by rt-PA, new therapeutic approaches for the treatment of occlusive thrombosis are being actively investigated. In this context, the study of Mangold et al is of critical interest as it designates NETs as a source of new biomarkers to define the biological process of acute coronary syndrome and DNA as a therapeutic target for increasing the efficacy of rt-PA–induced thrombus lysis. Furthermore, this study strengthens the idea that periodontal diseases can affect the development and evolution of atherothrombotic diseases.

Acknowledgments

We are indebted to Mary Osborne-Pellegrin and Richard Bayles for help in editing the article.

Sources of Funding

This study was supported by grants from Fondation de France (no. 2012-29500) and Fondation pour la Recherche Médicale.

Disclosures

None.

References


Key Words: Editorial. blood platelets. hemoglobins. infection. leukocytes.
Thrombi and Neutrophils
Jean-Baptiste Michel and Benoît Ho-Tin-Noé

*Circ Res.* 2015;116:1107-1108
doi: 10.1161/CIRCRESAHA.115.306050

*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/116/7/1107

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation Research* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation Research* is online at:
http://circres.ahajournals.org//subscriptions/